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(54) **Controlled absorption pharmaceutical composition.**

(57) A sustained absorption propranolol-containing pellet for oral administration comprises a core of propranolol or a pharmaceutically acceptable salt thereof and an organic acid embedded in a polymeric material in a multi-layer arrangement and an outer membrane which permits release of the propranolol at a controlled rate in an aqueous medium. The pellet has a dissolution rate *in vitro* in an aqueous medium, which when measured in a basket assembly according to U.S. Pharmacopoeia XX at 37°C and 75 r.p.m., is not more than 15% of the total propranol after 2 hours of measurement in a buffer solution at pH 7.5. Not more than 30% of the total propranolol is released after a total of 4 hours of measurement and not more than 63% of the total propranolol is released after a total of 6 hours.

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CONTROLLED ABSORPTION PHARMACEUTICAL COMPOSITION

This invention relates to controlled absorption pharmaceutical compositions and, in particular, to a controlled absorption propranolol composition.

Propranolol (1-(isopropylamino)-3-(1-naphthyloxy)-2-propanol) is a beta-adrenergic blocking agent and as such is a competitive inhibitor of the effects of catecholamines at beta-adrenergic receptor sites. The principal effect of propranolol is to reduce cardiac activity by diminishing or preventing beta-adrenergic stimulation. By reducing the rate and force of contraction of the heart, and decreasing the rate of conduction of impulses through the conducting system, the response of the heart to stress and exercise is reduced. These properties are used in the treatment of angina of effort to reduce the oxygen consumption and increase the exercise tolerance of the heart. Propranolol is also used in the treatment of cardiac arrhythmias to block adrenergic stimulation of cardiac pacemaker potentials. Propranolol is also beneficial in the long term treatment of hypertension. Other uses of propranolol are in the treatment of migraine and anxiety.

Propranolol is normally administered as propranolol hydrochloride tablets. Propranolol hydrochloride tablets are marketed by Imperial Chemical Industries PLC (ICI) under the trade mark Inderal. The normal dosage regimen is 10-40mg three or four times daily.

A major drawback of oral propranolol therapy is that propranolol is extensively and rapidly metabolised so that only a small proportion of the active ingredient reaches the systemic circulation

after oral administration. Propranolol is absorbed from the gastro-intestinal tract with peak plasma concentrations occurring one to two hours after a single dose. It is excreted in the urine as free and conjugated propranolol and as metabolites.

A sustained release form of Inderal for once daily administration is available and is marketed by ICI under the trade mark Inderal LA. This form of propranolol while exhibiting a sustained release of the drug has a relatively poor bioavailability. Furthermore, the absorption varies considerably from individual to individual. Other sustained release forms of propranolol are described in U.S. Patent Specification Nos. 4,248,857 and 4,248,858.

It is an object of the present invention to provide a controlled absorption form of propranolol which is suitable for once daily administration and which is characterised by a high extent of absorption, which is largely invariable from individual to individual, and hence by a high bioavailability.

Accordingly, the invention provides a controlled absorption propranolol-containing pellet for oral administration, said pellet comprising a core of propranolol or a pharmaceutically acceptable salt thereof and an organic acid embedded in a polymeric material in a multi-layer arrangement, and an outer membrane which permits release of the propranolol at a controlled rate in an aqueous medium, said pellet having a dissolution rate in a buffer solution at pH 7.5 which when measured in a basket assembly according to U.S. Pharmacopoeia XX at 37^{o}C and 75 r.p.m., has the following characteristics:

a) up to 15% of the total propranolol is released during the first two hours of measurement in said assembly;

b) between 15 and 30% of the total propranolol is released after a total of 4 hours of measurement in said assembly;

c) between 43 and 63% of the total propranolol is released after a total of 6 hours of measurement in said assembly;

d) between 75 and 100% of the total propranolol is released after a total of 8 hours of measurement in said assembly; and

e) between 85 and 100% of the total propranolol is released after a total of 10 hours of measurement in said assembly.

Preferably, the pellet contains propranolol hydrochloride.

Preferably, the organic acid is represented by one or more of the following acids: citric acid, tartaric acid, succinic acid, malic acid, ascorbic acid and fumaric acid.

The propranolol and organic acid are preferably present in a ratio of 2:1.

Preferably, the polymeric material in which the propranolol is embedded has a major proportion of a polymer which is rapidly soluble in water.

The polymeric material may consist solely of a water soluble polymer or, alternatively, it may include a minor proportion of a water insoluble polymer. The ratio of water soluble to water insoluble polymer is determined by the particular combination of polymers selected.

The water soluble polymer is suitably hydroxypropylmethylcellulose, polyvinylpyrrolidone or a polymer sold under the trade mark EUDRAGIT RL. Polymers sold under the Trade Mark EUDRAGIT are acrylic resins comprising copolymers of acrylic and methacrylic esters.

The water insoluble polymer is suitably a cellulose ether such as methyl-, ethyl- or propyl-cellulose, Shellac or a polymer sold under the trade mark EUDRAGIT RS. Shellac is a resinous excretion of the insect Laccifer (Tachardia) Lacca kerr, order Homoptera, family Coccidae.

The core will suitably have between 20 and 120 layers and is built up in a manner known per se.

Further, preferably, the multi-layer arrangement of propranolol, organic acid and polymeric material will be built up on a central inert core suitably consisting of a non-pareil seed having an average diameter in the range 0.3-0.7mm.

The outer membrane preferably includes a major proportion of a water insoluble polymer.

Further, the outer membrane suitably comprises a major proportion of a water insoluble polymer and a minor proportion of a water soluble polymer, the ratio of water insoluble to water soluble polymer being determined by the inherent solubility characteristics of the polymers selected.

Suitable combinations of water insoluble and water soluble polymers for the rate-controlling membrane include: ethylcellulose and hydroxypropyl-cellulose in a ratio of 9:1; EUDRAGIT RS AND EUDRAGIT RL in a ratio of 8:2 and Shellac and polyvinylpyrroli-idone in a ratio of 9:1.

The outer membrane is formed by applying a number of coats of a solution containing the or each polymer to the core as hereinafter described. Preferably, the number of coats of polymer solution applied is between 30 and 90 coats.

The pellets may be filled into hard gelatin capsules or compressed into tablets using a binder and/or hardening agent commonly employed in tabletting such as microcrystalline cellulose sold under the trade mark AVICEL or diisopropylbenzothiazyl-2-sulphenamide sold under the trade mark DIPAC, in such a way that the specific dissolution rate of the pellets is maintained.

The invention will be further illustrated by the following Examples.

EXAMPLE 1

Propranolol-containing pellets were prepared in the following manner.

(a) Powder Blend

Propranolol hydrochloride (# 100 mesh)(1,000g), talc (100g) and citric acid (500g) were blended in a standard pharmaceutical blender into a uniform powder.

(b) Polymer Solution

A solution of 8 parts (by volume) 10% hydroxypropylmethylcellulose (15 c.p.s.) in methanol/methylene chloride, 60:40 and 2 parts (by volume) 10% ethylcellulose (50 c.p.s.) in methanol/methylene chloride, 60:40 was prepared. Diethylphthalate as a plasticizer was included, as required.

(c) Membrane Solution

The membrane solution was prepared from the following ingredients:

1 part (by volume) 10% hydroxypropylmethylcellulose (15 c.p.s.) in methanol/methylene chloride, 60:40;

9 parts (by volume) 10% ethylcellulose (50 c.p.s.) in methanol/methylene chloride, 60:40;

10 parts (by volume) methanol/methylene chloride, 60:40;

10 parts (by weight) talc;
Diethylphthalate (plasticizer), as required.

Pellet Making Procedure

Step 1. 750g of starch/sugar seeds (0.4 to 0.5 mm diameter) were placed in a conventional coating pan and rotation was commenced.

Step 2. The seeds were wetted with sufficient polymer solution (b) to dampen them uniformly.

Step 3. Powder blend (a) was dusted on until no more adhered to the dampened seeds.

Step 4. The powder coated seeds were allowed to dry (5-15 minutes).

Steps 2-4 were repeated until all of the powder (a) had been coated on.

Step 5. The powder coated seeds were sealed with one application of polymer solution (b) and talc.

Step 6. The powder coated seeds were dried at 45-50°C in an oven for at least 12 hours.

Step 7. The powder coated seeds were placed in a conventional coating pan and rotation was commenced.

Step 8. A coat of membrane solution (c) was applied to the powder coated seeds and the seeds so coated were allowed to dry. A coat of membrane solution (c) corresponds to 10ml of solution (c) per 1,000g of coated seeds.

Step 9. Two further coats of membrane solution (c) were applied to the coated seeds.

Step 10. The finished pellets were allowed to dry at 45-50°C.

The dried pellets were subjected to a dissolution test as follows:

Apparatus:

A Basket Assembly as described in the United States Pharmacopoeia XX at 37°C and 75 r.p.m.

Buffer:

25ml of 2.0 M potassium chloride and 950ml of water was adjusted to pH 7.5 with either 0.1 N hydrochloric acid or 0.1 N sodium hydroxide and the volume made up to 1,000ml with water.

Sampling Times:

2, 4, 6, 8 and 10 hours.

Method:

2g of finished pellets were placed in the basket of the assembly and rotation was commenced in 1,000ml of buffer. At the sampling times, 1.0ml of the solution was removed and diluted to 50ml with 0.1 N hydrochloric acid. The absorbance of the sample was measured at 290nm in a spectrophotometer.

The absorbance value equivalent to 100% dissolution was determined by grinding 2g of pellets in 0.1 N hydrochloric acid, filtering , diluting a 1ml sample to 50ml with water and measuring the absorbance at 290nm as before. The percentage dissolution was calculated by division.

Steps 7 to 10 were repeated until the dissolution rate at pH 7.5 was as follows:

2 hours	0- 15%
4 hours	15- 30%
6 hours	43- 63%
8 hours	75-100%
10 hours	85-100%

A total of 45 coats of membrane solution (c) was applied before the required dissolution rate was obtained.

EXAMPLE 2

Propranolol-containing pellets were prepared in the following manner.

(a) Powder Blend

Propranolol hydrochloride (# 100 mesh)(1,000g), talc (100g) and ascorbic acid (500g) were blended in a standard pharmaceutical blender into a uniform powder.

(b) Polymer Solution

A solution of 7 parts (by volume) 5% EUDRAGIT RL in isopropanol/acetone, 60:40 and 3 parts 5% EUDRAGIT RS in isopropanol/acetone, 60:40 was prepared. Diethylphthalate (plasticizer) was included as required.

(c) Membrane Solution

The membrane solution was prepared from the following ingredients:

2 parts (by volume) 5% EUDRAGIT RL in isopropanol/acetone, 60:40;

8 parts (by volume) 5% EUDRAGIT RS in isopropanol/acetone, 60:40;

10 parts (by volume) isopropanol/acetone, 60:40;

10 parts (by weight) talc;

Diethylphthalate (plasticizer), as required.

Pellet Making Procedure

Steps 1-4 were carried out as in Example 1.

Steps 2-4 were repeated until all of the powder (a) had been coated on.

Step 5. The powder coated seeds were sealed with two applications of polymer solution (b) and talc.

Step 6. The powder coated seeds were oven dried at 45-50°C.

Step 7. The powder coated seeds were placed in a conventional coating pan and rotation was commenced.

Step 8. A coat of membrane solution (c) was applied to the powder coated seeds and the seeds so coated were allowed to dry. As in the case of Example 1 a coat of membrane solution (c) corresponds to 10ml of solution (c) per 1,000g of coated seeds.

Step 9. One further coat of membrane solution (c) was applied to the coated seeds.

Step 10. The finished pellets were allowed to dry at 45-50°C.

The dried pellets were subjected to the dissolution test as described in Example 1 and Steps 7-10 were repeated until the desired dissolution rate at pH 7.5 was obtained.

EXAMPLE 3

Propranolol-containing pellets were prepared in the following manner.

(a) Powder Blend

Propranolol hydrochloride (# 100 mesh)(1,000g), talc (100g) and fumaric acid (500g) were blended in a standard pharmaceutical blender into a uniform powder.

(b) Polymer Solution

A solution of 19 parts (by volume) 20% polyvinylpyrrolidone (Kollidon K-30; Kollidon K-30 is a trade mark) in isopropanol and 1 part (by volume) 33% Shellac (dewaxed) in ethanol was prepared.

(C) Membrane Solution

The membrane solution was prepared from the following ingredients.

1 part (by volume) 20% polyvinylpyrrolidone (Kollidon K-30) in isopropanol;

9 parts (by volume) 33% Shellac (dewaxed) in ethanol;

10 parts (by volume) isopropanol;

10 parts (by weight) talc;

Diethylphthalate (plasticizer), as required.

Pellet Making Procedure

Steps 1-4 were carried out as in Example 1.

Steps 2-4 were repeated until all of the powder (a) had been coated on.

Step 5. The powder coated seeds were sealed with one application of polymer solution (b) and talc.

Step 6. The powder coated seeds were oven dried at 45-50°C for at least 12 hours.

Step 7. The powder coated seeds were placed in a conventional coating pan and rotation was commenced.

Step 8. A coat of membrane solution (c) was applied to the powder coated seeds and the seeds so coated were allowed to dry. As in the case of Examples 1 and 2 above a coat of membrane solution (c) corresponds to 10ml of solution (c) per 1,000g of coated seeds.

Step 9. Two further coats of membrane solution (c) were applied to the coated seeds.

Step 10. The finished pellets were allowed to dry at 45-50°C.

The dried pellets were then subjected to a dissolution test as described in Example 1 above. Steps 7-10 were repeated until a satisfactory dissolution rate was obtained. A total of 60 coats of membrane solution (c) was applied before the required dissolution rate was obtained. The dissolution rate of the product was as follows:

2 hours	:	9.9%
4 hours	:	21.9%
6 hours	:	47.0%
8 hours	:	79.0%
10 hours	:	95.3%

Fig. 1 is a graph of percentage dissolution versus time of pellets according to the invention. Curve B shows the maximum percentage dissolution per unit time and Curve A the minimum percentage dissolution per unit time permissible to achieve a peak plasma level between 8 and 10 hours.

Fig 2. is a graph of plasma levels (ng/ml) versus time after administration (hours) for a single dose of pellets prepared according to Example 3 in tablet form (160mg)(+) compared with Inderal tablets (80mg)(*) administered at 0 and 12 hours.

The graphs of Fig. 2 were drawn from the mean values obtained for six subjects according to the data listed in Tables 1 and 2.

As will be observed from Fig. 2 peak plasma levels occurred at 2 and 2.8 hours after the first and second Inderal dose, respectively. The propranolol prepared according to Example 3 (160mg tablet) showed a peak plasma level at 8 hours.

Fig. 3 is a graph of plasma levels (ng/ml) versus time after administration (hours) for a single dose of pellets prepared according to Example 3 in tablet form (120mg)(+) compared with a single dose of Inderal LA tablets (160mg)(*).

The graphs of Fig. 3 were drawn from the mean values obtained for six subjects according to the data listed in Tables 3 and 4.

As will be observed from Fig. 3 Inderal LA showed a peak plasma level at 9.3 hours and the propranolol prepared according to Example 3 (120mg tablet) showed a peak plasma level at 8.7 hours.

TABLE 1

Inderal (80mg b.i.d.)

Blood level study results - Summary of pharmacokinetic data

	HOURS AFTER ADMINISTRATION															
SUBJ	0.00	2.00	3.00	4.00	5.00	6.00	8.00	10.00	12.00	13.00	14.00	15.00	16.00	24.00	36.00	AUC*
1	0.00	147.30	133.90	101.43	65.20	50.16	42.60	19.99	11.73	58.00	103.06	60.62	64.33	29.10	2.28	1,555.34
2	0.00	122.19	79.45	63.40	54.99	33.98	22.26	10.23	5.51	32.95	55.22	49.87	37.39	15.60	3.49	988.57
3	0.00	39.40	26.15	18.74	15.75	8.95	3.78	4.87	0.00	0.00	4.46	23.16	27.93	3.64	0.00	340.17
4	0.00	103.88	64.74	48.11	23.34	15.01	7.23	0.00	0.00	55.05	60.48	51.30	32.69	3.78	0.00	680.72
5	0.00	69.83	55.43	42.36	28.36	24.73	14.98	0.00	0.00	12.87	34.94	40.98	37.60	8.74	0.00	643.33
6	0.00	73.40	41.40	33.84	15.96	16.82	9.70	8.70	4.07	0.00	23.39	33.92	35.95	18.11	0.00	669.62
MEAN	0.00	92.67	66.84	51.31	33.93	24.94	16.76	7.30	3.55	26.48	46.92	43.31	39.31	13.16	0.96	812.96
ST DEV	0.00	39.27	37.67	28.69	21.06	15.09	14.21	7.54	4.67	26.23	34.36	13.46	12.78	9.83	1.54	417.69
**CV(%)	0.00	42.38	56.35	55.90	62.07	60.49	84.82	103.28	131.36	99.05	73.23	31.08	32.52	74.64	159.95	51.38
MAX	0.00	147.30	133.90	101.43	65.20	50.16	42.60	19.99	11.73	58.00	103.06	60.62	64.33	29.10	3.49	1,555.34
MIN	0.00	39.40	26.15	18.74	15.75	8.95	3.78	0.00	0.00	0.00	4.46	23.16	27.93	3.64	0.00	340.17

* Area under the curve.

**Coefficient of variation.

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Table 2

Controlled absorption propranolol prepared according to Example 3 (160mg)

Blood level study results - Summary of pharmacokinetic data

	HOURS AFTER ADMINISTRATION															
SUBJ	0.00	2.00	3.00	4.00	5.00	6.00	8.00	10.00	12.00	13.00	14.00	15.00	16.00	24.00	36.00	AUC*
1	0.00	12.01	16.74	27.58	35.64	113.98	86.80	82.03	55.56	47.03	43.59	57.28	47.86	15.76	0.00	1,210.81
2	0.00	2.21	5.57	12.13	39.47	48.72	49.55	182.14	125.91	94.25	68.19	58.30	47.94	16.10	1.08	1,389.76
3	0.00	0.00	9.66	8.14	18.11	55.99	75.48	50.29	44.96	35.60	28.54	21.38	20.56	9.74	1.32	722.23
4	0.00	6.98	4.37	6.73	16.64	30.91	33.67	28.79	24.62	23.25	17.76	14.52	12.72	4.80	3.43	427.77
5	0.00	3.68	4.11	4.05	16.58	24.56	35.83	33.47	27.85	17.45	20.63	13.65	14.71	8.04	6.02	481.92
6	0.00	4.64	4.47	8.24	13.89	23.17	68.92	45.61	37.73	25.23	20.25	15.58	21.00	7.05	24.68	728.11
MEAN	0.00	4.92	7.49	11.15	23.39	49.55	58.37	70.39	52.77	40.47	33.16	30.12	27.46	10.25	6.09	826.77
ST DEV	0.00	4.19	4.98	8.47	11.12	34.24	21.95	57.85	37.57	28.35	19.59	21.61	16.15	4.68	9.36	390.70
CV(%)	0.00	85.11	66.58	75.96	47.56	69.09	37.60	82.19	71.20	70.05	59.07	71.74	58.82	45.70	153.66	47.26
MAX	0.00	12.01	16.74	27.58	39.47	113.98	86.80	182.14	125.91	94.25	68.19	58.30	47.94	16.10	24.68	1,389.76
MIN	0.00	0.00	4.11	4.05	13.89	23.17	33.67	28.79	24.62	17.45	17.76	13.65	12.72	4.80	0.00	427.77

* Area under the curve.

**Coefficient of variation.

Table 3

Inderal LA - 160mg

Blood level study results - Summary of pharmacokinetic data

	HOURS AFTER ADMINISTRATION										
SUBJ	0.00	2.00	4.00	6.00	8.00	10.00	12.00	14.00	16.00	24.00	AUC*
1	0.00	0.00	0.00	5.05	9.64	7.34	7.13	9.36	2.10	0.00	87.54
2	0.00	1.78	0.50	2.28	1.65	2.77	3.29	2.48	2.46	1.35	47.20
3	0.00	0.96	3.73	8.14	19.41	21.79	24.85	22.76	17.08	15.44	350.44
4	0.00	17.44	27.11	30.33	31.81	27.46	19.68	17.18	16.44	7.19	452.98
5	0.00	1.11	4.19	5.00	9.44	9.48	8.95	5.19	7.40	2.78	134.84
6	0.00	13.23	23.45	42.30	29.84	25.59	19.83	16.26	9.92	7.71	421.44
MEAN	0.00	5.75	9.83	15.52	16.97	15.74	13.96	12.21	9.23	5.75	249.08
ST DEV	0.00	7.56	12.14	16.65	12.14	10.48	8.62	7.80	6.54	5.67	179.69
**CV(%)	0.00	131.43	123.49	107.32	71.56	66.58	61.76	63.94	70.87	98.73	72.14
MAX	0.00	17.44	27.11	42.30	31.81	27.46	24.85	22.76	17.08	15.44	452.98
MIN	0.00	0.00	0.00	2.28	1.65	2.77	3.29	2.48	2.10	0.01	47.20

* Area under the curve.

**Coefficient of variation.

Table 4

Controlled absorption Propranolol prepared according to Example 3 (120mg)

Blood level study results - Summary of pharmacokinetic data

	HOURS AFTER ADMINISTRATION										
SUBJ	0.00	2.00	4.00	6.00	8.00	10.00	12.00	14.00	16.00	24.00	AUC*
1	0.00	0.00	6.43	20.31	69.20	68.80	45.67	34.97	10.72	1.47	550.24
2	0.00	0.94	11.10	31.15	15.05	13.53	9.96	8.10	5.89	2.86	220.55
3	0.00	4.36	5.13	16.60	56.13	69.30	63.61	46.29	47.51	16.08	824.71
4	0.00	5.71	12.76	19.47	26.55	49.56	29.99	16.86	11.02	8.43	410.62
5	0.00	0.00	2.73	22.59	40.60	41.54	33.90	26.95	12.89	4.12	417.55
6	0.00	6.34	15.35	59.75	90.11	72.66	44.00	35.57	23.46	9.90	804.46
MEAN	0.00	2.89	8.92	28.31	49.61	52.56	37.86	28.12	18.58	7.14	538.02
ST DEV	0.00	2.92	4.89	16.18	27.83	22.81	17.99	13.87	15.32	5.46	238.69
**CV(%)	0.00	100.85	54.88	57.14	56.11	43.40	47.52	49.31	82.43	76.37	44.36
MAX	0.00	6.34	15.35	59.75	90.11	72.66	63.61	46.29	47.51	16.08	824.71
MIN	0.00	0.00	2.73	16.60	15.05	13.53	9.96	8.10	5.89	1.47	220.55

* Area under the curve.

**Coefficient of variation.

The blood level studies carried out and the results of which are given in Tables 1-4 showed that a 160mg single dose of the propranolol prepared according to Example 3 had an equivalent plasma level AUC (area under the curve)(826.8ng h/ml) as conventional Inderal tablets given at a dosage of 80mg at 0 and 12 hours (813.0 ng h/ml). In contrast, a 120mg single dose of the propranolol prepared according to Example 3 had a markedly higher plasma level AUC (538.0 ng h/ml) than a 160mg single dose of Inderal LA (249.1ng h/ml).

The propranolol of Example 3 showed a peak plasma level (85.0ng/ml) intermediate the first and second Inderal peak values viz 92.7 ng/ml and 53.9 ng/ml respectively. In contrast, the propranolol of Example 3 (120mg) had a markedly higher peak plasma level (58.5ng/ml) than Inderal LA (160mg) which had a peak plasma level of 20.2ng/ml.

In terms of variability, the propranolol of Example 3 was similar to Inderal in:

1) AUC variability

Propranolol of Example 3	%CV= 47.3
Inderal	%CV= 51.4;

2) Variability over sample points

Propranolol of Example 3	%CV= 71.0
Inderal	%CV= 76.2.

However, the propranolol of Example 3 was far less variable than Inderal LA for parameters 1) and 2):

1) AUC variability

Propranolol of Example 3	%CV= 44.4
Inderal LA	%CV= 72.2

2) Variability over sample points

Propranolol of Example 3	%CV= 63.1
Inderal LA	%CV= 88.4

In terms of time-cover (length of time with a particular level of drug) over a range of plasma propranolol levels, the propranolol of Example 3 was

equivalent to Inderal but even at a reduced dosage (120mg) it was far superior to Inderal LA as shown in Table 5:

Table 5

Propranolol Level (ng/ml)	Time Cover (h)			
	Propranolol of Ex. 3 (160mg)	Inderal (80mg x 2)	Propranolol of Ex. 3 (120mg)	Inderal LA (160mg)
20.0	13.0	15.0	9.8	4.1
40.0	6.3	6.0	4.9	0.1
60.0	2.8	2.7	2.0	0

For two different drugs to be equally effective or for two different formulations of the same drug to be equally effective, not only must the intensity of the effect be the same (related to concentration) but also the duration of effect (related to duration of time cover at effective concentrations).

In order to demonstrate equivalence of two different formulations, therapeutic equivalence is presumed to follow from equivalence of plasma levels. The parameters regarded as important in defining plasma levels include AUC, Cmax (peak levels), Tmax (time of peak levels) and also "time coverage". In the case of a controlled or sustained release formulation this latter parameter is of particular importance because although the shape of the plasma level curve is deliberately altered it is important that the total length of time that a relevant plasma concentration is maintained should be similar for the sustained-release formulation and the standard product.

In the case of propranolol, a definitive "therapeutic" plasma concentration range has not yet been described. However, a comparison of time-coverage at plasma values in the range 20-40-60 ng/ml

which cover the range of plasma levels observed following standard propranolol administration will allow a statement as to the equivalence or lack of equivalence of the products at levels that must include therapeutically important concentrations.

The data in Table 5 indicate the equivalence of the propranolol of Example 3 with conventional Inderal tablets and the much poorer performance of Inderal LA.

It will be appreciated from the foregoing description that the pellets according to the invention are more readily absorbed than conventional sustained release propranolol and that they exhibit excellent bioavailability.

CLAIMS:-

1. A sustained absorption propranolol-containing pellet for oral administration, characterised in that the pellet has a core of propranolol or a pharmaceutically acceptable salt thereof and an organic acid embedded in a polymeric material in a multi-layer arrangement and an outer membrane which permits release of the propranolol at a controlled rate in an aqueous medium, said pellet having a dissolution rate in a buffer solution at pH 7.5 which when measured in a basket assembly according to U.S. Pharmacopoeia XX at 37°C and 75 r.p.m., has the following characteristics:

a) up to 15% of the total propranolol is released during the first two hours of measurement in said assembly;

b) between 15 and 30% of the total propranolol is released after a total of 4 hours of measurement in said assembly;

c) between 43 and 63% of the total propranolol is released after a total of 6 hours of measurement in said assembly;

d) between 75 and 100% of the total propranolol is released after a total of 8 hours of measurement in said assembly; and

e) between 85 and 100% of the total propranolol is released after a total of 10 hours of measurement in said assembly.

2. A pellet according to Claim 1, wherein the organic acid is citric acid, tartaric acid, succinic acid, malic acid, ascorbic acid or fumaric acid or a mixture thereof.

3. A pellet according to Claim 1 or 2, characterised in that the polymeric material of the core includes a major proportion of a polymer which is rapidly soluble in water, especially hydroxypropyl-methylcellulose, polyvinylpyrrolidone or EUDRAGIT RL.

4. A pellet according to any one of Claims 1-3, which includes a minor proportion of a water-insoluble polymer, especially methylcellulose, ethylcellulose, propylcellulose, Shellac or EUDRAGIT RS, the ratio of water-soluble to water-insoluble polymer being determined by the inherent solubility characteristics of the polymers selected.

5. A pellet according to any preceding claim, wherein the multi-layer arrangement of propanolol, organic acid and polymeric material is built up on an inert core in a manner known per se, the core preferably having between 20 and 120 layers.

6. A pellet according to any preceding claim, wherein the outer membrane includes a major proportion of a water-insoluble polymer and a minor proportion of a water-soluble polymer, the ratio of water-insoluble to water-soluble polymer being determined by the inherent solubility characteristics of the polymers selected.

7. A pellet according to any preceding claim, characterised in that the outer membrane consists of:

ethylcellulose and hydroxypropylcellulose in a ratio of 9:1; EUDRAGIT RS and EUDRAGIT RL in a ratio of 8:2; or Shellac and polyvinylpyrrolidone in a ratio of 9:1.

8. A pellet according to any preceding claim, characterised in that the outer membrane is formed by applying a number of coats, preferably 30-90 coats, of a solution containing the or each polymer to the core.

9. A capsule or tablet comprising pellets according to any one of the preceding claims.

10. A process for the production of a pellet according to any one of claims 1-8 comprising forming a core of propranolol or a pharmaceutically acceptable salt thereof and an organic acid embedded in a polymeric material in a multi-layer arrangement and enclosing the core in an outer membrane which permits release of the propranolol in the manner set out in claim 1.

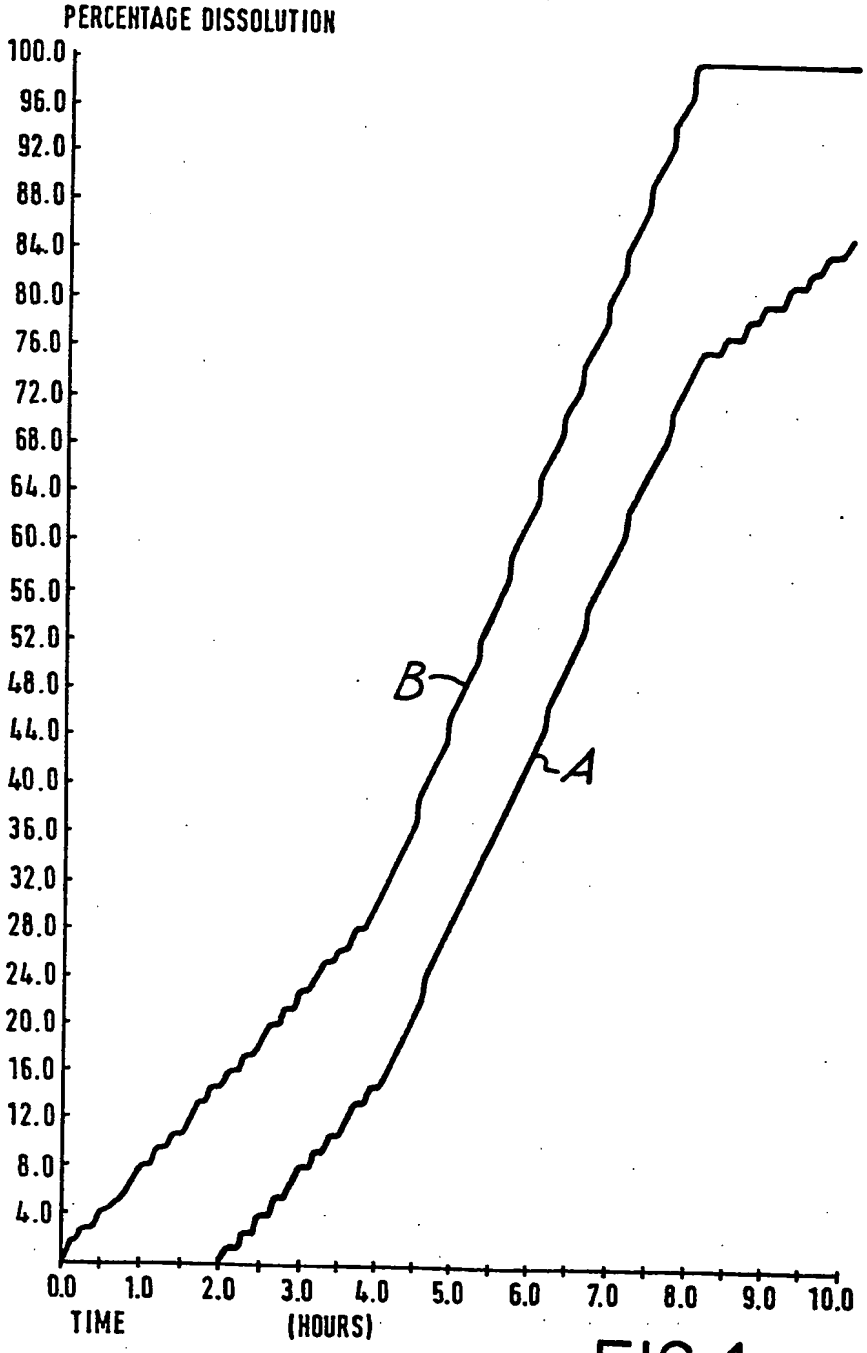
PERCENTAGE DISSOLUTION
100.0
96.0
92.0
88.0
84.0
80.0
76.0
72.0
68.0
64.0
60.0
56.0
52.0
48.0
44.0
40.0
36.0
32.0
28.0
24.0
20.0
16.0
12.0
8.0
4.0
B
A
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
TIME
(HOURS)

FIG. 1

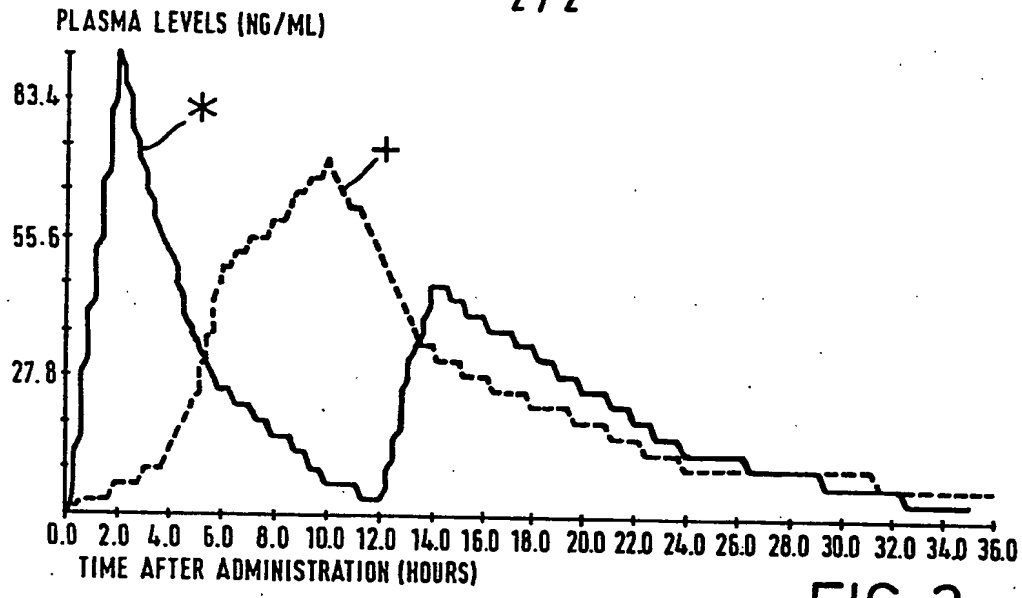
PLASMA LEVELS (NG/ML)
83.4
55.6
27.8
0.0 2.0 4.0 6.0 8.0 10.0 12.0 14.0 16.0 18.0 20.0 22.0 24.0 26.0 28.0 30.0 32.0 34.0 36.0
TIME AFTER ADMINISTRATION (HOURS)

FIG.2

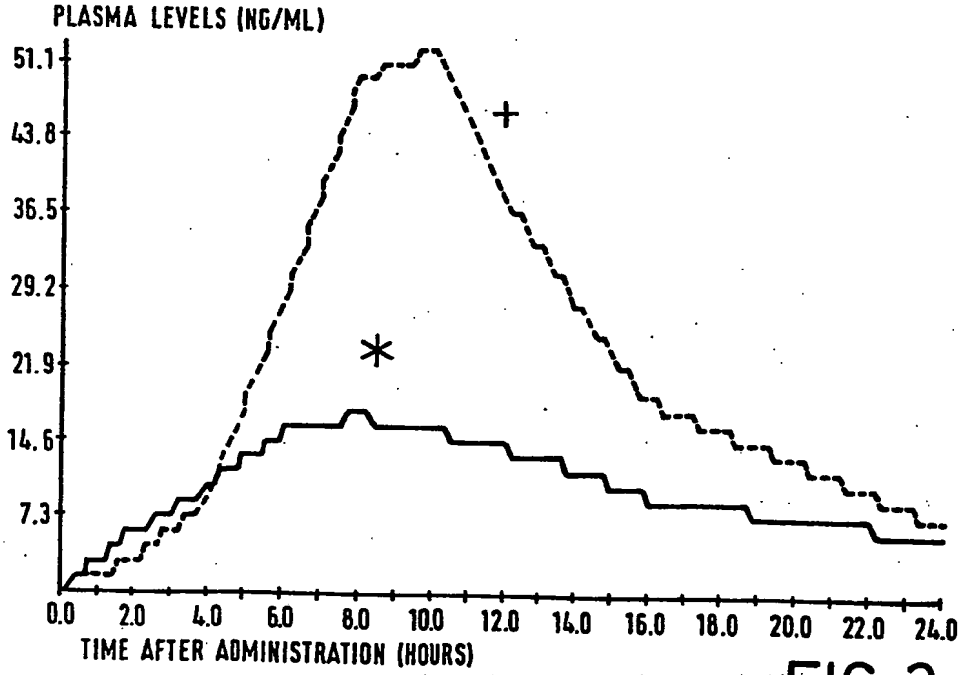
PLASMA LEVELS (NG/ML)
51.1
43.8
36.5
29.2
21.9
14.6
7.3
0.0 2.0 4.0 6.0 8.0 10.0 12.0 14.0 16.0 18.0 20.0 22.0 24.0
TIME AFTER ADMINISTRATION (HOURS)

FIG.3

European Patent Office

EUROPEAN SEARCH REPORT

0123470
Application number

EP 84302385.4

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
A	US - A - 4 309 406 (P.C. GULEY et al.) * Examples; claims * --	1,3,4	A 61 K 31/135 A 61 K 9/22 A 61 K 9/24 A 61 K 9/26
A	US - A - 4 309 404 (R.J. DE NEALE et al.) * Examples; claims * --	1,3,4	
D,A	US - A - 4 248 858 (P.C. GULEY et al.) * Examples; claims * --	1,3,4	
D,A	US - A - 4 248 857 (R.J. DE NEALE et al.) * Examples; claims * --	1,3,4	
A	US - A - 4 248 856 (P.C. GULEY et al.) * Examples; claims * ----	1,3,4	

TECHNICAL FIELDS SEARCHED (Int. Cl. ³)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	05-07-1984	SLAMA

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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(54) **Controlled absorption pharmaceutical composition.**

(57) A sustained absorption propranolol-containing pellet for oral administration comprises a core of propranolol or a pharmaceutically acceptable salt thereof and an organic acid embedded in a polymeric material in a multi-layer arrangement and an outer membrane which permits release of the propranolol at a controlled rate in an aqueous medium. The pellet has a dissolution rate *in vitro* in an aqueous medium, which when measured in a basket assembly according to U.S. Pharmacopoeia XX at 37°C and 75 r.p.m., is not more than 15% of the total propranol after 2 hours of measurement in a buffer solution at pH 7.5. Not more than 30% of the total propranolol is released after a total of 4 hours of measurement and not more than 63% of the total propranolol is released after a total of 6 hours.

EP 0 123 470 A1

0123470

CONTROLLED ABSORPTION PHARMACEUTICAL COMPOSITION

This invention relates to controlled absorption pharmaceutical compositions and, in particular, to a controlled absorption propranolol composition.

Propranolol (1-(isopropylamino)-3-(1-naphthyloxy)-2-propanol) is a beta-adrenergic blocking agent and as such is a competitive inhibitor of the effects of catecholamines at beta-adrenergic receptor sites. The principal effect of propranolol is to reduce cardiac activity by diminishing or preventing beta-adrenergic stimulation. By reducing the rate and force of contraction of the heart, and decreasing the rate of conduction of impulses through the conducting system, the response of the heart to stress and exercise is reduced. These properties are used in the treatment of angina of effort to reduce the oxygen consumption and increase the exercise tolerance of the heart. Propranolol is also used in the treatment of cardiac arrhythmias to block adrenergic stimulation of cardiac pacemaker potentials. Propranolol is also beneficial in the long term treatment of hypertension. Other uses of propranolol are in the treatment of migraine and anxiety.

Propranolol is normally administered as propranolol hydrochloride tablets. Propranolol hydrochloride tablets are marketed by Imperial Chemical Industries PLC (ICI) under the trade mark Inderal. The normal dosage regimen is 10-40mg three or four times daily.

A major drawback of oral propranolol therapy is that propranolol is extensively and rapidly metabolised so that only a small proportion of the active ingredient reaches the systemic circulation

after oral administration. Propranolol is absorbed from the gastro-intestinal tract with peak plasma concentrations occurring one to two hours after a single dose. It is excreted in the urine as free and conjugated propranolol and as metabolites.

A sustained release form of Inderal for once daily administration is available and is marketed by ICI under the trade mark Inderal LA. This form of propranolol while exhibiting a sustained release of the drug has a relatively poor bioavailability. Furthermore, the absorption varies considerably from individual to individual. Other sustained release forms of propranolol are described in U.S. Patent Specification Nos. 4,248,857 and 4,248,858.

It is an object of the present invention to provide a controlled absorption form of propranolol which is suitable for once daily administration and which is characterised by a high extent of absorption, which is largely invariable from individual to individual, and hence by a high bioavailability.

Accordingly, the invention provides a controlled absorption propranolol-containing pellet for oral administration, said pellet comprising a core of propranolol or a pharmaceutically acceptable salt thereof and an organic acid embedded in a polymeric material in a multi-layer arrangement, and an outer membrane which permits release of the propranolol at a controlled rate in an aqueous medium, said pellet having a dissolution rate in a buffer solution at pH 7.5 which when measured in a basket assembly according to U.S. Pharmacopoeia XX at 37°C and 75 r.p.m., has the following characteristics:

a) up to 15% of the total propranolol is released during the first two hours of measurement in said assembly;

b) between 15 and 30% of the total propranolol is released after a total of 4 hours of measurement in said assembly;

c) between 43 and 63% of the total propranolol is released after a total of 6 hours of measurement in said assembly;

d) between 75 and 100% of the total propranolol is released after a total of 8 hours of measurement in said assembly; and

e) between 85 and 100% of the total propranolol is released after a total of 10 hours of measurement in said assembly.

Preferably, the pellet contains propranolol hydrochloride.

Preferably, the organic acid is represented by one or more of the following acids: citric acid, tartaric acid, succinic acid, malic acid, ascorbic acid and fumaric acid.

The propranolol and organic acid are preferably present in a ratio of 2:1.

Preferably, the polymeric material in which the propranolol is embedded has a major proportion of a polymer which is rapidly soluble in water.

The polymeric material may consist solely of a water soluble polymer or, alternatively, it may include a minor proportion of a water insoluble polymer. The ratio of water soluble to water insoluble polymer is determined by the particular combination of polymers selected.

The water soluble polymer is suitably hydroxypropylmethylcellulose, polyvinylpyrrolidone or a polymer sold under the trade mark EUDRAGIT RL. Polymers sold under the Trade Mark EUDRAGIT are acrylic resins comprising copolymers of acrylic and methacrylic esters.

The water insoluble polymer is suitably a cellulose ether such as methyl-, ethyl- or propyl-cellulose, Shellac or a polymer sold under the trade mark EUDRAGIT RS. Shellac is a resinous excretion of the insect Laccifer (Tachardia) Lacca kerr, order Homoptera, family Coccidae.

The core will suitably have between 20 and 120 layers and is built up in a manner known per se.

Further, preferably, the multi-layer arrangement of propranolol, organic acid and polymeric material will be built up on a central inert core suitably consisting of a non-pareil seed having an average diameter in the range 0.3-0.7mm.

The outer membrane preferably includes a major proportion of a water insoluble polymer.

Further, the outer membrane suitably comprises a major proportion of a water insoluble polymer and a minor proportion of a water soluble polymer, the ratio of water insoluble to water soluble polymer being determined by the inherent solubility characteristics of the polymers selected.

Suitable combinations of water insoluble and water soluble polymers for the rate-controlling membrane include: ethylcellulose and hydroxypropyl-cellulose in a ratio of 9:1; EUDRAGIT RS AND EUDRAGIT RL in a ratio of 8:2 and Shellac and polyvinylpyrrol-idone in a ratio of 9:1.

The outer membrane is formed by applying a number of coats of a solution containing the or each polymer to the core as hereinafter described. Preferably, the number of coats of polymer solution applied is between 30 and 90 coats.

The pellets may be filled into hard gelatin capsules or compressed into tablets using a binder and/or hardening agent commonly employed in tabletting such as microcrystalline cellulose sold under the trade mark AVICEL or diisopropylbenzothiazyl-2-sulphenamide sold under the trade mark DIPAC, in such a way that the specific dissolution rate of the pellets is maintained.

The invention will be further illustrated by the following Examples.

EXAMPLE 1

Propranolol-containing pellets were prepared in the following manner.

(a) Powder Blend

Propranolol hydrochloride (# 100 mesh)(1,000g), talc (100g) and citric acid (500g) were blended in a standard pharmaceutical blender into a uniform powder.

(b) Polymer Solution

A solution of 8 parts (by volume) 10% hydroxypropylmethylcellulose (15 c.p.s.) in methanol/methylene chloride, 60:40 and 2 parts (by volume) 10% ethylcellulose (50 c.p.s.) in methanol/methylene chloride, 60:40 was prepared. Diethylphthalate as a plasticizer was included, as required.

(c) Membrane Solution

The membrane solution was prepared from the following ingredients:

1 part (by volume) 10% hydroxypropylmethylcellulose (15 c.p.s.) in methanol/methylene chloride, 60:40;

9 parts (by volume) 10% ethylcellulose (50 c.p.s.) in methanol/methylene chloride, 60:40;

10 parts (by volume) methanol/methylene chloride, 60:40;

10 parts (by weight) talc;
Diethylphthalate (plasticizer), as required.

Pellet Making Procedure

Step 1. 750g of starch/sugar seeds (0.4 to 0.5 mm diameter) were placed in a conventional coating pan and rotation was commenced.

Step 2. The seeds were wetted with sufficient polymer solution (b) to dampen them uniformly.

Step 3. Powder blend (a) was dusted on until no more adhered to the dampened seeds.

Step 4. The powder coated seeds were allowed to dry (5-15 minutes).

Steps 2-4 were repeated until all of the powder (a) had been coated on.

Step 5. The powder coated seeds were sealed with one application of polymer solution (b) and talc.

Step 6. The powder coated seeds were dried at 45-50°C in an oven for at least 12 hours.

Step 7. The powder coated seeds were placed in a conventional coating pan and rotation was commenced.

Step 8. A coat of membrane solution (c) was applied to the powder coated seeds and the seeds so coated were allowed to dry. A coat of membrane solution (c) corresponds to 10ml of solution (c) per 1,000g of coated seeds.

Step 9. Two further coats of membrane solution (c) were applied to the coated seeds.

Step 10. The finished pellets were allowed to dry at 45-50°C.

The dried pellets were subjected to a dissolution test as follows:

Apparatus:

A Basket Assembly as described in the United States Pharmacopoeia XX at 37°C and 75 r.p.m.

Buffer:

25ml of 2.0 M potassium chloride and 950ml of water was adjusted to pH 7.5 with either 0.1 N hydrochloric acid or 0.1 N sodium hydroxide and the volume made up to 1,000ml with water.

Sampling Times:

2, 4, 6, 8 and 10 hours.

Method:

2g of finished pellets were placed in the basket of the assembly and rotation was commenced in 1,000ml of buffer. At the sampling times, 1.0ml of the solution was removed and diluted to 50ml with 0.1 N hydrochloric acid. The absorbance of the sample was measured at 290nm in a spectrophotometer.

The absorbance value equivalent to 100% dissolution was determined by grinding 2g of pellets in 0.1 N hydrochloric acid, filtering , diluting a 1ml sample to 50ml with water and measuring the absorbance at 290nm as before. The percentage dissolution was calculated by division.

Steps 7 to 10 were repeated until the dissolution rate at pH 7.5 was as follows:

2 hours	0- 15%
4 hours	15- 30%
6 hours	43- 63%
8 hours	75-100%
10 hours	85-100%

A total of 45 coats of membrane solution (c) was applied before the required dissolution rate was obtained.

EXAMPLE 2

Propranolol-containing pellets were prepared in the following manner.

(a) Powder Blend

Propranolol hydrochloride (# 100 mesh)(1,000g), talc (100g) and ascorbic acid (500g) were blended in a standard pharmaceutical blender into a uniform powder.

(b) Polymer Solution

A solution of 7 parts (by volume) 5% EUDRAGIT RL in isopropanol/acetone, 60:40 and 3 parts 5% EUDRAGIT RS in isopropanol/acetone, 60:40 was prepared. Diethylphthalate (plasticizer) was included as required.

(c) Membrane Solution

The membrane solution was prepared from the following ingredients:

2 parts (by volume) 5% EUDRAGIT RL in isopropanol/acetone, 60:40;

8 parts (by volume) 5% EUDRAGIT RS in isopropanol/acetone, 60:40;

10 parts (by volume) isopropanol/acetone, 60:40;

10 parts (by weight) talc;

Diethylphthalate (plasticizer), as required.

Pellet Making Procedure

Steps 1-4 were carried out as in Example 1.

Steps 2-4 were repeated until all of the powder (a) had been coated on.

Step 5. The powder coated seeds were sealed with two applications of polymer solution (b) and talc.

Step 6. The powder coated seeds were oven dried at 45-50°C.

Step 7. The powder coated seeds were placed in a conventional coating pan and rotation was commenced.

Step 8. A coat of membrane solution (c) was applied to the powder coated seeds and the seeds so coated were allowed to dry. As in the case of Example 1 a coat of membrane solution (c) corresponds to 10ml of solution (c) per 1,000g of coated seeds.

Step 9. One further coat of membrane solution (c) was applied to the coated seeds.

Step 10. The finished pellets were allowed to dry at 45-50°C.

The dried pellets were subjected to the dissolution test as described in Example 1 and Steps 7-10 were repeated until the desired dissolution rate at pH 7.5 was obtained.

EXAMPLE 3

Propranolol-containing pellets were prepared in the following manner.

(a) Powder Blend

Propranolol hydrochloride (# 100 mesh)(1,000g), talc (100g) and fumaric acid (500g) were blended in a standard pharmaceutical blender into a uniform powder.

(b) Polymer Solution

A solution of 19 parts (by volume) 20% polyvinylpyrrolidone (Kollidon K-30; Kollidon K-30 is a trade mark) in isopropanol and 1 part (by volume) 33% Shellac (dewaxed) in ethanol was prepared.

(C) Membrane Solution

The membrane solution was prepared from the following ingredients.

1 part (by volume) 20% polyvinylpyrrolidone (Kollidon K-30) in isopropanol;

9 parts (by volume) 33% Shellac (dewaxed) in ethanol;

10 parts (by volume) isopropanol;

10 parts (by weight) talc;

Diethylphthalate (plasticizer), as required.

Pellet Making Procedure

Steps 1-4 were carried out as in Example 1.

Steps 2-4 were repeated until all of the powder (a) had been coated on.

Step 5. The powder coated seeds were sealed with one application of polymer solution (b) and talc.

Step 6. The powder coated seeds were oven dried at 45-50°C for at least 12 hours.

Step 7. The powder coated seeds were placed in a conventional coating pan and rotation was commenced.

Step 8. A coat of membrane solution (c) was applied to the powder coated seeds and the seeds so coated were allowed to dry. As in the case of Examples 1 and 2 above a coat of membrane solution (c) corresponds to 10ml of solution (c) per 1,000g of coated seeds.

Step 9. Two further coats of membrane solution (c) were applied to the coated seeds.

Step 10. The finished pellets were allowed to dry at 45-50°C.

The dried pellets were then subjected to a dissolution test as described in Example 1 above. Steps 7-10 were repeated until a satisfactory dissolution rate was obtained. A total of 60 coats of membrane solution (c) was applied before the required dissolution rate was obtained. The dissolution rate of the product was as follows:

2 hours	:	9.9%
4 hours	:	21.9%
6 hours	:	47.0%
8 hours	:	79.0%
10 hours	:	95.3%

Fig. 1 is a graph of percentage dissolution versus time of pellets according to the invention. Curve B shows the maximum percentage dissolution per unit time and Curve A the minimum percentage dissolution per unit time permissible to achieve a peak plasma level between 8 and 10 hours.

Fig 2. is a graph of plasma levels (ng/ml) versus time after administration (hours) for a single dose of pellets prepared according to Example 3 in tablet form (160mg)(+) compared with Inderal tablets (80mg)(*) administered at 0 and 12 hours.

The graphs of Fig. 2 were drawn from the mean values obtained for six subjects according to the data listed in Tables 1 and 2.

As will be observed from Fig. 2 peak plasma levels occurred at 2 and 2.8 hours after the first and second Inderal dose, respectively. The propranolol prepared according to Example 3 (160mg tablet) showed a peak plasma level at 8 hours.

Fig. 3 is a graph of plasma levels (ng/ml) versus time after administration (hours) for a single dose of pellets prepared according to Example 3 in tablet form (120mg)(+) compared with a single dose of Inderal LA tablets (160mg)(*).

The graphs of Fig. 3 were drawn from the mean values obtained for six subjects according to the data listed in Tables 3 and 4.

As will be observed from Fig. 3 Inderal LA showed a peak plasma level at 9.3 hours and the propranolol prepared according to Example 3 (120mg tablet) showed a peak plasma level at 8.7 hours.

TABLE 1

Inderal (80mg b.i.d.)

Blood level study results - Summary of pharmacokinetic data

	HOURS AFTER ADMINISTRATION															
SUBJ	0.00	2.00	3.00	4.00	5.00	6.00	8.00	10.00	12.00	13.00	14.00	15.00	16.00	24.00	36.00	AUC*
1	0.00	147.30	133.90	101.43	65.20	50.16	42.60	19.99	11.73	58.00	103.06	60.62	64.33	29.10	2.28	1,555.34
2	0.00	122.19	79.45	63.40	54.99	33.98	22.26	10.23	5.51	32.95	55.22	49.87	37.39	15.60	3.49	988.57
3	0.00	39.40	26.15	18.74	15.75	8.95	3.78	4.87	0.00	0.00	4.46	23.16	27.93	3.64	0.00	340.17
4	0.00	103.88	64.74	48.11	23.34	15.01	7.23	0.00	0.00	55.05	60.48	51.30	32.69	3.78	0.00	680.72
5	0.00	69.83	55.43	42.36	28.36	24.73	14.98	0.00	0.00	12.87	34.94	40.98	37.60	8.74	0.00	643.33
6	0.00	73.40	41.40	33.84	15.96	16.82	9.70	8.70	4.07	0.00	23.39	33.92	35.95	18.11	0.00	669.62
MEAN	0.00	92.67	66.84	51.31	33.93	24.94	16.76	7.30	3.55	26.48	46.92	43.31	39.31	13.16	0.96	812.96
ST DEV	0.00	39.27	37.67	28.69	21.06	15.09	14.21	7.54	4.67	26.23	34.36	13.46	12.78	9.83	1.54	417.69
**CV(%)	0.00	42.38	56.35	55.90	62.07	60.49	84.82	103.28	131.36	99.05	73.23	31.08	32.52	74.64	159.95	51.38
MAX	0.00	147.30	133.90	101.43	65.20	50.16	42.60	19.99	11.73	58.00	103.06	60.62	64.33	29.10	3.49	1,555.34
MIN	0.00	39.40	26.15	18.74	15.75	8.95	3.78	0.00	0.00	0.00	4.46	23.16	27.93	3.64	0.00	340.17

* Area under the curve.

**Coefficient of variation.

12-1

Table 2

Controlled absorption propranolol prepared according to Example 3 (160mg)

Blood level study results - Summary of pharmacokinetic data

	HOURS AFTER ADMINISTRATION															
SUBJ	0.00	2.00	3.00	4.00	5.00	6.00	8.00	10.00	12.00	13.00	14.00	15.00	16.00	24.00	36.00	AUC*
1	0.00	12.01	16.74	27.58	35.64	113.98	86.80	82.03	55.56	47.03	43.59	57.28	47.86	15.76	0.00	1,210.81
2	0.00	2.21	5.57	12.13	39.47	48.72	49.55	182.14	125.91	94.25	68.19	58.30	47.94	16.10	1.08	1,389.76
3	0.00	0.00	9.66	8.14	18.11	55.99	75.48	50.29	44.96	35.60	28.54	21.38	20.56	9.74	1.32	722.23
4	0.00	6.98	4.37	6.73	16.64	30.91	33.67	28.79	24.62	23.25	17.76	14.52	12.72	4.80	3.43	427.77
5	0.00	3.68	4.11	4.05	16.58	24.56	35.83	33.47	27.85	17.45	20.63	13.65	14.71	8.04	6.02	481.92
6	0.00	4.64	4.47	8.24	13.89	23.17	68.92	45.61	37.73	25.23	20.25	15.58	21.00	7.05	24.68	728.11
MEAN	0.00	4.92	7.49	11.15	23.39	49.55	58.37	70.39	52.77	40.47	33.16	30.12	27.46	10.25	6.09	826.77
ST DEV	0.00	4.19	4.98	8.47	11.12	34.24	21.95	57.85	37.57	28.35	19.59	21.61	16.15	4.68	9.36	390.70
CV(%)	0.00	85.11	66.58	75.96	47.56	69.09	37.60	82.19	71.20	70.05	59.07	71.74	58.82	45.70	153.66	47.26
MAX	0.00	12.01	16.74	27.58	39.47	113.98	86.80	182.14	125.91	94.25	68.19	58.30	47.94	16.10	24.68	1,389.76
MIN	0.00	0.00	4.11	4.05	13.89	23.17	33.67	28.79	24.62	17.45	17.76	13.65	12.72	4.80	0.00	427.77

* Area under the curve.

**Coefficient of variation.

Table 3

Inderal LA - 160mg

Blood level study results - Summary of pharmacokinetic data

	HOURS AFTER ADMINISTRATION										
SUBJ	0.00	2.00	4.00	6.00	8.00	10.00	12.00	14.00	16.00	24.00	AUC*
1	0.00	0.00	0.00	5.05	9.64	7.34	7.13	9.36	2.10	0.00	87.54
2	0.00	1.78	0.50	2.28	1.65	2.77	3.29	2.48	2.46	1.35	47.20
3	0.00	0.96	3.73	8.14	19.41	21.79	24.85	22.76	17.08	15.44	350.44
4	0.00	17.44	27.11	30.33	31.81	27.46	19.68	17.18	16.44	7.19	452.98
5	0.00	1.11	4.19	5.00	9.44	9.48	8.95	5.19	7.40	2.78	134.84
6	0.00	13.23	23.45	42.30	29.84	25.59	19.83	16.26	9.92	7.71	421.44
MEAN	0.00	5.75	9.83	15.52	16.97	15.74	13.96	12.21	9.23	5.75	249.08
ST DEV	0.00	7.56	12.14	16.65	12.14	10.48	8.62	7.80	6.54	5.67	179.69
**CV(%)	0.00	131.43	123.49	107.32	71.56	66.58	61.76	63.94	70.87	98.73	72.14
MAX	0.00	17.44	27.11	42.30	31.81	27.46	24.85	22.76	17.08	15.44	452.98
MIN	0.00	0.00	0.00	2.28	1.65	2.77	3.29	2.48	2.10	0.01	47.20

* Area under the curve.

**Coefficient of variation.

Table 4

Controlled absorption Propranolol prepared according to Example 3 (120mg)

Blood level study results - Summary of pharmacokinetic data

	HOURS AFTER ADMINISTRATION										
SUBJ	0.00	2.00	4.00	6.00	8.00	10.00	12.00	14.00	16.00	24.00	AUC*
1	0.00	0.00	6.43	20.31	69.20	68.80	45.67	34.97	10.72	1.47	550.24
2	0.00	0.94	11.10	31.15	15.05	13.53	9.96	8.10	5.89	2.86	220.55
3	0.00	4.36	5.13	16.60	56.13	69.30	63.61	46.29	47.51	16.08	824.71
4	0.00	5.71	12.76	19.47	26.55	49.56	29.99	16.86	11.02	8.43	410.62
5	0.00	0.00	2.73	22.59	40.60	41.54	33.90	26.95	12.89	4.12	417.55
6	0.00	6.34	15.35	59.75	90.11	72.66	44.00	35.57	23.46	9.90	804.46
MEAN	0.00	2.89	8.92	28.31	49.61	52.56	37.86	28.12	18.58	7.14	538.02
ST DEV	0.00	2.92	4.89	16.18	27.83	22.81	17.99	13.87	15.32	5.46	238.69
**CV(%)	0.00	100.85	54.88	57.14	56.11	43.40	47.52	49.31	82.43	76.37	44.36
MAX	0.00	6.34	15.35	59.75	90.11	72.66	63.61	46.29	47.51	16.08	824.71
MIN	0.00	0.00	2.73	16.60	15.05	13.53	9.96	8.10	5.89	1.47	220.55

* Area under the curve.

**Coefficient of variation.

The blood level studies carried out and the results of which are given in Tables 1-4 showed that a 160mg single dose of the propranolol prepared according to Example 3 had an equivalent plasma level AUC (area under the curve)(826.8ng h/ml) as conventional Inderal tablets given at a dosage of 80mg at 0 and 12 hours (813.0 ng h/ml). In contrast, a 120mg single dose of the propranolol prepared according to Example 3 had a markedly higher plasma level AUC (538.0 ng h/ml) than a 160mg single dose of Inderal LA (249.1ng h/ml).

The propranolol of Example 3 showed a peak plasma level (85.0ng/ml) intermediate the first and second Inderal peak values viz 92.7 ng/ml and 53.9 ng/ml respectively. In contrast, the propranolol of Example 3 (120mg) had a markedly higher peak plasma level (58.5ng/ml) than Inderal LA (160mg) which had a peak plasma level of 20.2ng/ml.

In terms of variability, the propranolol of Example 3 was similar to Inderal in:

1) AUC variability

Propranolol of Example 3	%CV= 47.3
Inderal	%CV= 51.4;

2) Variability over sample points

Propranolol of Example 3	%CV= 71.0
Inderal	%CV= 76.2.

However, the propranolol of Example 3 was far less variable than Inderal LA for parameters 1) and 2):

1) AUC variability

Propranolol of Example 3	%CV= 44.4
Inderal LA	%CV= 72.2

2) Variability over sample points

Propranolol of Example 3	%CV= 63.1
Inderal LA	%CV= 88.4

In terms of time-cover (length of time with a particular level of drug) over a range of plasma propranolol levels, the propranolol of Example 3 was

equivalent to Inderal but even at a reduced dosage (120mg) it was far superior to Inderal LA as shown in Table 5:

Table 5

Propranolol Level (ng/ml)	Time Cover (h)			
	Propranolol of Ex. 3 (160mg)	Inderal (80mg x 2)	Propranolol of Ex. 3 (120mg)	Inderal LA (160mg)
20.0	13.0	15.0	9.8	4.1
40.0	6.3	6.0	4.9	0.1
60.0	2.8	2.7	2.0	0

For two different drugs to be equally effective or for two different formulations of the same drug to be equally effective, not only must the intensity of the effect be the same (related to concentration) but also the duration of effect (related to duration of time cover at effective concentrations).

In order to demonstrate equivalence of two different formulations, therapeutic equivalence is presumed to follow from equivalence of plasma levels. The parameters regarded as important in defining plasma levels include AUC, Cmax (peak levels), Tmax (time of peak levels) and also "time coverage". In the case of a controlled or sustained release formulation this latter parameter is of particular importance because although the shape of the plasma level curve is deliberately altered it is important that the total length of time that a relevant plasma concentration is maintained should be similar for the sustained-release formulation and the standard product.

In the case of propranolol, a definitive "therapeutic" plasma concentration range has not yet been described. However, a comparison of time-coverage at plasma values in the range 20-40-60 ng/ml

which cover the range of plasma levels observed following standard propranolol administration will allow a statement as to the equivalence or lack of equivalence of the products at levels that must include therapeutically important concentrations.

The data in Table 5 indicate the equivalence of the propranolol of Example 3 with conventional Inderal tablets and the much poorer performance of Inderal LA.

It will be appreciated from the foregoing description that the pellets according to the invention are more readily absorbed than conventional sustained release propranolol and that they exhibit excellent bioavailability.

CLAIMS:-

1. A sustained absorption propranolol-containing pellet for oral administration, characterised in that the pellet has a core of propranolol or a pharmaceutically acceptable salt thereof and an organic acid embedded in a polymeric material in a multi-layer arrangement and an outer membrane which permits release of the propranolol at a controlled rate in an aqueous medium, said pellet having a dissolution rate in a buffer solution at pH 7.5 which when measured in a basket assembly according to U.S. Pharmacopoeia XX at 37°C and 75 r.p.m., has the following characteristics:

a) up to 15% of the total propranolol is released during the first two hours of measurement in said assembly;

b) between 15 and 30% of the total propranolol is released after a total of 4 hours of measurement in said assembly;

c) between 43 and 63% of the total propranolol is released after a total of 6 hours of measurement in said assembly;

d) between 75 and 100% of the total propranolol is released after a total of 8 hours of measurement in said assembly; and

e) between 85 and 100% of the total propranolol is released after a total of 10 hours of measurement in said assembly.

2. A pellet according to Claim 1, wherein the organic acid is citric acid, tartaric acid, succinic acid, malic acid, ascorbic acid or fumaric acid or a mixture thereof.

3. A pellet according to Claim 1 or 2, characterised in that the polymeric material of the core includes a major proportion of a polymer which is rapidly soluble in water, especially hydroxypropyl-methylcellulose, polyvinylpyrrolidone or EUDRAGIT RL.

4. A pellet according to any one of Claims 1-3, which includes a minor proportion of a water-insoluble polymer, especially methylcellulose, ethylcellulose, propylcellulose, Shellac or EUDRAGIT RS, the ratio of water-soluble to water-insoluble polymer being determined by the inherent solubility characteristics of the polymers selected.

5. A pellet according to any preceding claim, wherein the multi-layer arrangement of propanolol, organic acid and polymeric material is built up on an inert core in a manner known per se, the core preferably having between 20 and 120 layers.

6. A pellet according to any preceding claim, wherein the outer membrane includes a major proportion of a water-insoluble polymer and a minor proportion of a water-soluble polymer, the ratio of water-insoluble to water-soluble polymer being determined by the inherent solubility characteristics of the polymers selected.

7. A pellet according to any preceding claim, characterised in that the outer membrane consists of:

ethylcellulose and hydroxypropylcellulose in a ratio of 9:1; EUDRAGIT RS and EUDRAGIT RL in a ratio of 8:2; or Shellac and polyvinylpyrrolidone in a ratio of 9:1.

8. A pellet according to any preceding claim, characterised in that the outer membrane is formed by applying a number of coats, preferably 30-90 coats, of a solution containing the or each polymer to the core.

9. A capsule or tablet comprising pellets according to any one of the preceding claims.

10. A process for the production of a pellet according to any one of claims 1-8 comprising forming a core of propranolol or a pharmaceutically acceptable salt thereof and an organic acid embedded in a polymeric material in a multi-layer arrangement and enclosing the core in an outer membrane which permits release of the propranolol in the manner set out in claim 1.

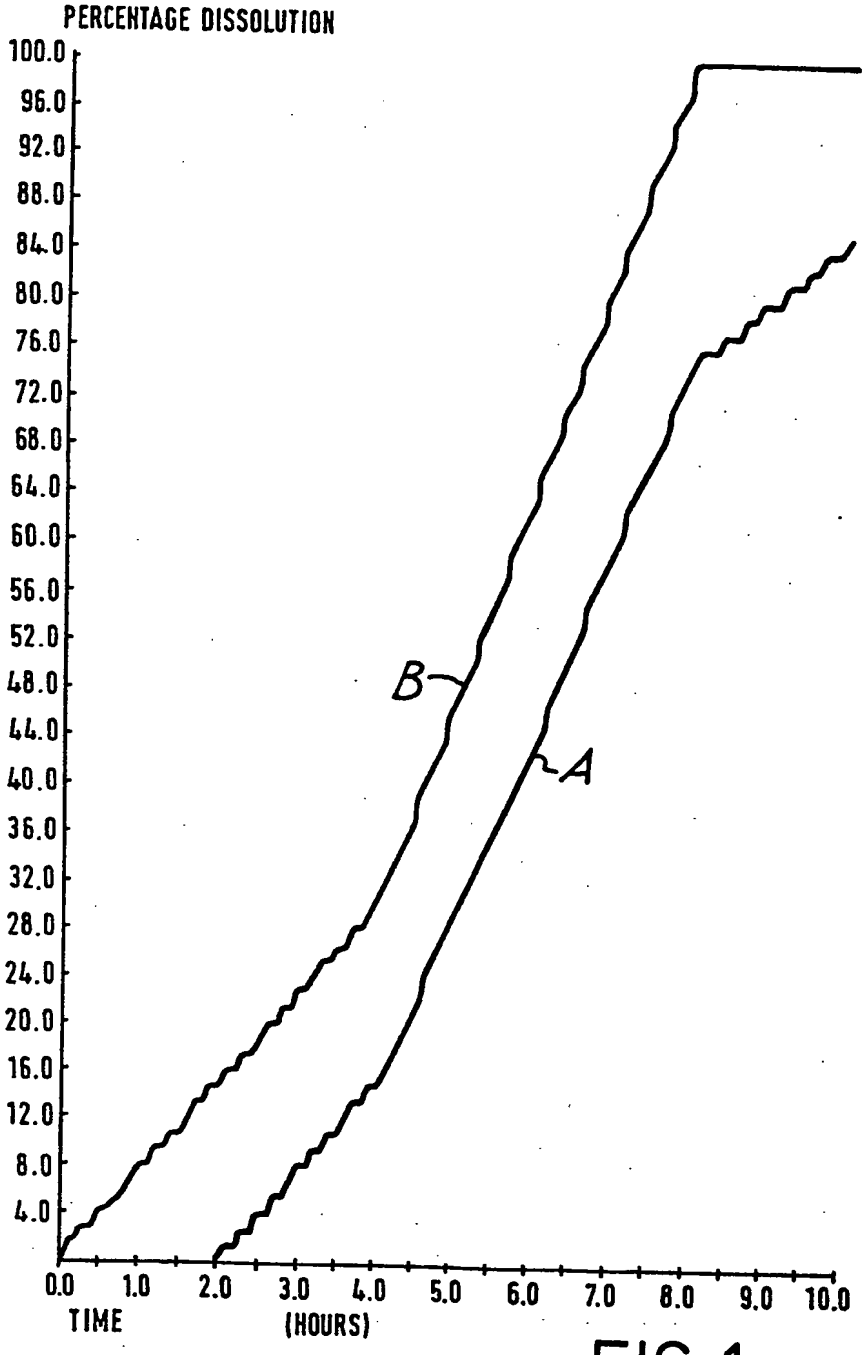
PERCENTAGE DISSOLUTION
100.0
96.0
92.0
88.0
84.0
80.0
76.0
72.0
68.0
64.0
60.0
56.0
52.0
48.0
44.0
40.0
36.0
32.0
28.0
24.0
20.0
16.0
12.0
8.0
4.0
B
A
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
TIME
(HOURS)

FIG. 1

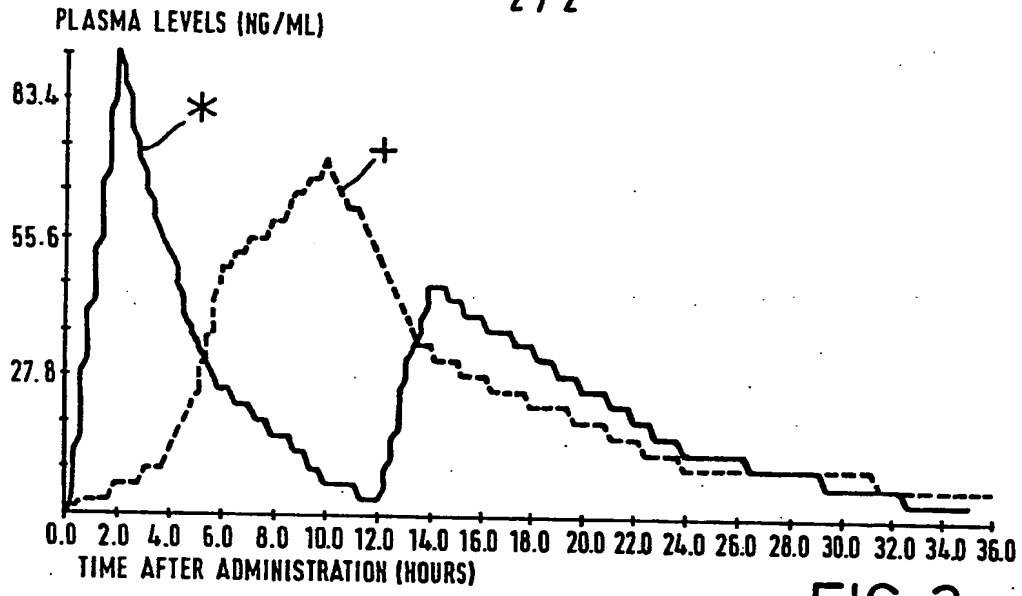
PLASMA LEVELS (NG/ML)
83.4
55.6
27.8
0.0 2.0 4.0 6.0 8.0 10.0 12.0 14.0 16.0 18.0 20.0 22.0 24.0 26.0 28.0 30.0 32.0 34.0 36.0
TIME AFTER ADMINISTRATION (HOURS)

FIG.2

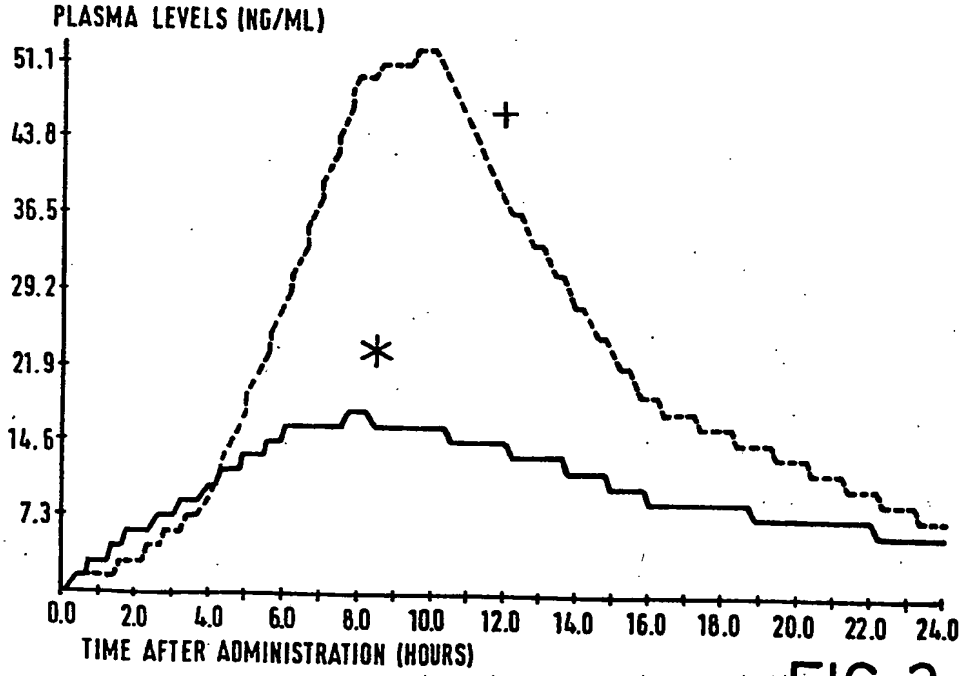
PLASMA LEVELS (NG/ML)
51.1
43.8
36.5
29.2
21.9
14.6
7.3
0.0 2.0 4.0 6.0 8.0 10.0 12.0 14.0 16.0 18.0 20.0 22.0 24.0
TIME AFTER ADMINISTRATION (HOURS)

FIG.3

European Patent Office

EUROPEAN SEARCH REPORT

0123470
Application number

EP 84302385.4

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
A	US - A - 4 309 406 (P.C. GULEY et al.) * Examples; claims * --	1,3,4	A 61 K 31/135 A 61 K 9/22 A 61 K 9/24 A 61 K 9/26
A	US - A - 4 309 404 (R.J. DE NEALE et al.) * Examples; claims * --	1,3,4	
D,A	US - A - 4 248 858 (P.C. GULEY et al.) * Examples; claims * --	1,3,4	
D,A	US - A - 4 248 857 (R.J. DE NEALE et al.) * Examples; claims * --	1,3,4	
A	US - A - 4 248 856 (P.C. GULEY et al.) * Examples; claims * ----	1,3,4	TECHNICAL FIELDS SEARCHED (Int. Cl. ³) A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	05-07-1984	SLAMA

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